

EDITORIAL COMMENT

The Curse of Target Lesion Calcification

Still Active After All These Years*

David D. Waters, MD,[†] Rabih R. Azar, MD, MSc[‡]
San Francisco, California; and Beirut, Lebanon



At the dawn of interventional cardiology, Andreas Grüntzig remarked that balloon angioplasty was limited by anatomic factors such as fibrotic or calcified stenoses (1). Subsequently, in large series of patients undergoing balloon angioplasty, coronary calcification was one of the factors associated with a lack of initial success (2). Techniques such as higher inflation pressures and rotational atherectomy were developed in part to deal with heavily calcified lesions. With the advent of coronary stents, it was rapidly appreciated that heavy calcification could interfere with full stent expansion (3). In the long-term follow-up of patients with drug-eluting stents, moderate-to-severe target lesion calcification (TLC) was one of the independent predictors of stent thrombosis (4).

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In this issue of the *Journal*, Généreux et al. (5) reported on the frequency and clinical impact of coronary calcification among patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) in 2 large clinical trials. Severe or moderate TLC was present in 5.9% and 26.1% of 6,855 patients, respectively, and was associated in univariate analysis with significantly higher rates of death, cardiac death, stent thrombosis, and ischemic target lesion and target vessel revascularization at 1 year compared with patients with mild or no TLC. These findings may not be surprising but are important because the frequency and effect of TLC in patients with ACS undergoing PCI have not previously been reported in a large cohort with structured follow-up and with TLC assessed uniformly by a core laboratory.

Several points merit further discussion.

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From the [†]Division of Cardiology, San Francisco General Hospital and University of California, San Francisco School of Medicine, San Francisco, California; and the [‡]Division of Cardiology, Hôtel Dieu de France Hospital and Saint-Joseph University School of Medicine, Beirut, Lebanon. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Coronary calcium and plaque rupture. The traditional view held that coronary calcification is more likely to be associated with stable as compared with unstable coronary lesions (6) and that lipid pools, but not calcium, increase stress and instability of coronary plaques (7). More recent evidence indicates that microcalcifications within the fibrous cap increase stress and plaque instability (8,9). Such microcalcifications are too small to be viewed by the usual techniques; however, by intravascular ultrasound (IVUS), most rupture-prone plaques show speckled or diffuse calcification (10).

In this context, the high rates of TLC in this study were unexpected: 27% of patients with non-ST-segment elevation ACS and 38% of patients with ST-segment elevation myocardial infarction (STEMI) had 1 or more moderately or severely calcified target lesions treated with PCI. This degree of calcification, because it is grossly visible by fluoroscopy, is much more severe than the diffuse speckled calcifications seen with IVUS (10) or the microcalcification seen in tissue samples with high-resolution imaging (9). A partial explanation for the high prevalence of TLC in this study is that the lesions treated with PCI might not always correspond to the culprit lesion responsible for the ACS event; indeed, the number of treated lesions per patient ranged from 1.31 to 1.40, depending on the category of calcification. Nevertheless, the traditional concept, that plaque rupture occurs in lipid-laden lesions without calcium and that calcified lesions are relatively safe, appears to be an oversimplification.

Affixing blame: the patient, the lesion, or the stent?

Patients with moderate or severe TLC in this study were older, had more renal insufficiency, had lower ejection fractions, and were more likely to have had a STEMI compared with patients with no or mild TLC. Thus, if moderate or severe TLC by itself had no effect on the immediate and long-term effects of PCI, these patients would still be likely to have a worse outcome due to these adverse clinical features.

On the other hand, lesions with moderate or severe TLC also have other characteristics that are unfavorable, including longer lesion length, more total occlusions, more visible thrombi, and more triple-vessel disease. If patients with more TLC had clinical features similar to patients with no or mild TLC, their post-PCI prognosis would still be worse because of their unfavorable lesion features. After the procedure, Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 had been attained in 93.1% of patients with no or mild TLC, 91.6% of those with moderate TLC, and only 85.9% of those with severe TLC ($p < 0.0001$). This alone presages a worse prognosis for the latter group.

But what about the stent itself? Calcification may prevent complete expansion of the stent or interfere with stent delivery, resulting in damage either to the structure of the stent or to the polymer in the case of drug-eluting stents. A malapposed, incompletely expanded, or damaged stent increases the risks for stent thrombosis and target lesion

revascularization. In this study, these were the 2 endpoints that TLC predicted by multivariate analysis.

Compared with fluoroscopy, IVUS provides far more information about TLC. In one series of 110 patients undergoing PCI, fluoroscopy detected TLC in approximately one-half of the patients, whereas IVUS detected TLC in about three-quarters (11). TLC was categorized by IVUS according to the number of quadrants involved, superficial or deep involvement, and axial length of calcification. Such information should be helpful in planning the type of intervention.

Coronary calcification is also an adverse prognostic factor in patients undergoing coronary bypass surgery. In a companion study to this one (12), with the same core laboratory to categorize coronary calcification, severe calcification was present in 13.6% of patients before bypass surgery and was an independent predictor of major adverse cardiac events at 1 year (hazard ratio: 1.77; 95% confidence interval: 1.18 to 2.66; $p = 0.006$).

Coronary calcification is associated with aortic valve calcification, mitral annular calcification, and calcification of the thoracic aorta (13). Calcification of the thoracic aorta has been shown to be a strong predictor of cardiovascular events and death in patients with stable angina (13).

Practical implications. As the authors point out, interventional cardiologists tend to underestimate the degree of TLC. Would recognition of TLC improve outcomes? IVUS guidance to confirm optimal stent expansion and apposition and to check for hidden dissection might improve outcomes (14) and would be most appropriate for heavily calcified lesions. TLC correlates with increased platelet reactivity despite aspirin and clopidogrel use (15). The use of more potent antiplatelet drugs such as prasugrel or ticagrelor instead of clopidogrel might be warranted for heavily calcified lesions, although this has not been proven.

In conclusion, Généreux et al. have done us a service by highlighting the continuing bad consequences of TLC. Despite huge advances in PCI technology over nearly 50 years, the curse of calcification persists.

Reprint requests and correspondence: Dr. David D. Waters, Division of Cardiology, San Francisco General Hospital, 1001 Potrero Avenue, San Francisco, California 94114. E-mail: dwaters@medsfgh.ucsf.edu.

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